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The Management of Neuroleptic-Induced CNS Effects

SUMMARY

Basal ganglia side effects caused by the neuroleptic drugs include the acute extrapyramidal syndromes (dystonias, akathisia and parkinsonism) and tardive dyskinesia. These may be ignored, misdiagnosed or mistreated by the patient or physician. Because the neuroleptics are effective in the treatment and secondary prevention of serious psychiatric disorders such as schizophrenia, it is important that neurological side effects be anticipated and appropriately managed. This increases patient compliance and enhances the therapeutic relationship. Patients should be examined frequently and systematically for basal ganglia side effects. (Can Fam Physician 1981; 27:1615-1624).

SOMMAIRE

Les effets secondaires sur les noyaux gris centraux causés par les neuroleptiques comprennent les syndromes extrapyramidaux aigus (dystonies, akathisie et parkinsonisme) et la dyskinésie tardive. Il arrive que les médecins (et les patients) ne connaissent pas ces effets secondaires et fassent une erreur en les diagnostiquant et en les traitant. En raison de l'efficacité des neuroleptiques dans le traitement et la prévention secondaire de troubles psychiatriques graves comme la schizophrénie, il est important de prévoir les effets secondaires neurologiques et de savoir comment y remédier. Cela augmente la participation du patient et améliore la relation thérapeutique. Les patients doivent être examinés fréquemment et systématiquement pour que soient décelés les effets secondaires sur les noyaux gris centraux.

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THE WIDESPREAD use of antipsychotic medications in clinical psychiatry has created new problems for the family physician. These include the neurological motor disturbances of parkinsonism and tardive dyskinesia (TD). Both syndromes are neuroleptic-induced consequences of interference in the balance of cholinergic and dopaminergic mechanisms in the nigrostriatum.[1] Neuroleptics affect several neurotransmitter systems, but appear to exert their clinical effects via dopamine receptor blockade.[1] This prevents dopaminergic transmission and for the short term mimics the dopamine deficiency state of Parkinson's disease. CNS dopamine fibers are believed to be inhibitory in the nigrostriatum and are balanced by excitatory acetylcholine-mediated neurons. Thus, acetylcholine predominance secondary to neuroleptic blockade produces the three cardinal signs of tremor, rigidity and akinesia typical of parkinsonism. Consequently treatment for drug-induced parkinsonism requires either decreasing the dopamine blockade (by lowering the dose of neuroleptic or giving a dopamine agonist) or re-establishing the dopamine/acetylcholine balance by the addition of an anticholinergic drug.

Longterm dopaminergic blockade leads to the hyperkinetic state (especially in the orobuccal area) called tardive dyskinesia.[1,2] As a result of chronic dopamine antagonism by maintenance neuroleptics, the striatal neurons synthesize more neuroleptic-dopamine receptors.[1,3] thus increasing the response to whatever dopamine manages to bypass the neuroleptic blockade. Striatal dopaminergic neurons are thus overstimulated in relation to cholinergic neurons. Unlike parkinsonism, tardive dyskinesia is aggravated at least temporarily by lowering the neuroleptic dose and allowing more dopamine through. It is also aggravated by anticholinergic drugs, which decrease acetylcholine activity and cause further dopamine/acetylcholine imbal-

ance.[4] Thus, the two syndromes are clinically similar in some ways but require diametrically opposed treatment strategies.

Definition and Prevalence

Extrapyramidal side effects (EPS) from the neuroleptics may be classified[5] as:

Acute
Dystonia
Akathisia
Parkinsonism
—rigidity
—akinesia
—tremor
Chronic
Tardive dyskinesia

Acute dystonic reactions are of sudden onset and consist of painful, muscular spasms and contractures, usually involving the muscles of the head and neck. They frequently occur within 24-48 hours after starting or increasing the dose of a neuroleptic. Akathisia refers to the subjective desire to be in motion with a consequent inability to sit or stand still. The restless leg syndrome is part of this condition. Drug-induced parkinsonism, already described, consists of akinesia, tremor and rigidity. It and acute dystonia are usually dose-related: the higher the dose, the greater the likelihood of side effects. In some instances, they may occur at low doses, an expression of special vulnerability.

Tardive dyskinesia is a syndrome of involuntary hypermotility of the facial muscles and extremities, appearing as a late effect of neuroleptic therapy, although a few cases with early onset have been reported.[6] This syndrome differs from acute neuroleptic-induced motor disorders by its slow and insidious onset, its aggravation by anti-cholinergic drugs and its increased intensity upon the initial withdrawal of neuroleptics. Although the syndrome is usually reversible,[7] it may persist for months, years or even indefinitely[5] after neuroleptics are withdrawn.

At the usual clinical doses, 40-50% of patients on oral neuroleptics and 90% of patients on depot fluphenazine develop acute parkinsonism, dystonia or akathisia. Depending on the population studied, 0.5%-56% of patients maintained on these medications exhibit signs of tardive dyskinesia.[9] In general, the older the population on neuroleptics, the more closely the prevalence approximates the larger percentage.

Ayd[8] found acute extrapyramidal side effects .in 38.5% of his patients on neuroleptics and recorded their distribution: dystonias (2.3%), akathisia (21.2%), and parkinsonism (15%). These percentages have not changed significantly in the last 20 years. Dystonias are more common in young males (male:female ratio is 2:1) and they occur rapidly—90% occur within 72 hours of starting drug therapy. Akathisia, akinesia and parkinsonism are more frequent in females and occur later (90% occur within three months of starting treatment). The incidence of these side effects is related not only to dose and to individual sensitivities but also to the type of neuroleptic used. On average, the prevalence of acute side effects is twice as high in women.[9] However, the meaning of this ratio is unclear, since women are believed to be prescribed higher doses of neuroleptics and to be more compliant.

Tardive dyskinesia (TD) is more closely related to the duration of treatment with neuroleptics than to the dose. Feminine gender, a history of head injury or previous cerebral damage, depot neuroleptics, the use of anticholinergic drugs, and especially increasing age all predispose to tardive dyskinesia.[9] Despite equivalent total neuroleptic dose, 50% of patients never develop TD which suggests that only some individuals are susceptible. The exact nature of the susceptibility is as yet unknown.[10] The signs of tardive dyskinesia may be masked by the presence of neuroleptics and may become manifest only when the neuroleptic is decreased or when an anticholinergic agent is added.

Examination

Acute Basal Ganglia Side Effects

A thorough history and examination is needed to distinguish these side effects from other organic or functional syndromes.

Akinesia, as a side effect of the neuroleptics, may be misdiagnosed as depression, residual schizophrenic defect or demoralization. Akathisia may be mistaken for decompensating psychosis or anxiety, and dystonias may be confused with psychogenic motor disorders. Subjective distress secon-

dary to the side effects of the acetylcholine-dopamine imbalance in the basal ganglia needs to be distinguished from hypochondriasis, general complaintiveness and/or rationalization for neuroleptic refusal among psychiatric patients.

Acute EPS may be present at rest and is aggravated by anxiety and alertness. Acetylcholine released in the striatum is increased by stimulation of the reticular formation of the brain stem as well as by the substantia nigra, cortex and caudate. Thus both cortical (cognitive) and reticular (emotional) stimuli may increase the acetylcholine/dopamine imbalance and effectively aggravate extrapyramidal signs and symptoms.[1] These signs are decreased by intention, purposeful movement, sleep and relaxation. Examinations must therefore be repeated frequently to allow for fluctuations in these signs. A complete examination needs to be systematic.

Head and Neck. Drug-induced parkinsonism is characterized by masked facies and rigidity of facial muscles, both at rest and during active movements such as talking or smiling. The patient finds it difficult to wrinkle his forehead or to whistle. Blinking is infrequent and the mouth may remain closed even while the patient is talking. When the forehead just above the bridge of the nose (the glabellar area) is tapped with a reflex hammer or a finger, a normal person will blink (even when told not to) for the first one to five consecutive taps. A person with EPS will continue to blink, sometimes indefinitely. Six to ten consecutive blinks indicate mild side effects; 11-20 consecutive blinks, moderate; 21+ consecutive blinks, severe. The jaw may be rigid. Tongue fasciculations, excess salivation or drooling may occur. Dysarthria may be a feature. Rigidity of the neck muscles may be observed on passive movements of the neck.

Limbs. Each limb should be examined separately. Hypertonus of the shoulder girdle can be elicited by passive flexion and rotation of the humerus. The elbow and wrist muscles should each be examined for hypertonus and cogwheel rigidity by moving the joints passively through all directions. The examiner should break this rhythm to make sure that active movements do not mask the rigidity and cogwheeling, which is most noticeable when the movements are truly passive. A resting tremor may be masked if the patient holds a cigaret or grasps his knees or the arms of his chair. An intention tremor is elicited if a patient is asked to write his name or draw a spiral. Also, if the examiner and the patient hold each other's arms straight out at eye level, the examiner can compare the "arm drop" by noting the slap on the thigh, the rebound and the speed of the patient's arm drop, comparing these to his own.

Gait. The gait of EPS is often typical—a slow, stooped shuffling gait with loss of associated movements of the arms and markedly increased flexion angle at the elbow. This is marked when the patient turns, which needs more coordination of opposing muscle groups. Propulsion and retropulsion can also occur. In addition, akathisia can be noted by the continuous tapping of the patient's feet, his relentless need to pace and the twisting of his fingers.

Dystonias or neck muscle spasms (torticollis), the back (scoliosis, lordosis) and the pelvis (tortipelvis) may be present, and be confused with epileptic seizures or psychogenic symptoms. One example is opisthotonos, which is a painful tetanic spasm in which the patient's head and spine are bent backwards, lifting the patient's back off the bed. In addition, painful tonic contractions of the jaw (trismus) or eye muscles (oculogyric crises) can frequently occur. Clonic movements can be seen in individual muscle groups of the chest, back, abdomen or extremities. Dystonias are often very dramatic, very painful and are sometimes life threatening when they affect respiratory function.

Tardive Dyskinesia

The signs of tardive dyskinesia are disorders of movement rather than tone, therefore observation alone is adequate examination. This is best done when the patient's attention is directed elsewhere, because conscious attention to the movements inhibits them. Most of the signs occur above the neck. The buccolingual-masticatory (BLM) triad is most frequently seen: sucking and smacking movements of the lips, lateral jaw movements, and tongue thrusting or fly-catching movements. Spasmodic blinking, twitching, snarling and grunting may also occur. These signs disappear in sleep. Characteristically,

movements are irregular and spasmodic; the patient may be unaware of them, even when they are quite marked. Peripherally, the most common signs are athetotic movements of the fingers, knees, toes, shoulders, pelvis or spine which are uncoordinated, and arrhythmic. They may be accompanied by respiratory grunts.

When the causative neuroleptic is discontinued, the syndrome worsens initially, then improves and gradually disappears over several weeks or months.[7, 10] Sometimes it persists and irreversible neuronal degeneration may occur.

Treatment for Basal Ganglia Side Effects

1. *Education and reassurance:* In the acute phase of treatment with neuroleptics, the patient should be forewarned that side effects may occur, and that he should report them early. Most side effects remit spontaneously within a few days or weeks; medication is available for the more serious ones. The patient can be told that he will not become addicted to either the neuroleptic or the side effect medication and, in fact, the side effect medication will probably not be needed after a few weeks. Patients and their families should also be educated about the early signs of tardive dyskinesia.

2. *Neuroleptic dose decrease:* This is often the best treatment if the symptoms that warranted the use of a neuroleptic are under control. With acute EPS, the symptoms will improve within a week after a dose decrease. In early tardive dyskinesia, after a dose decrease, the signs will temporarily get worse but should improve in four to six weeks. The physician and the patient must weigh the advantages of a decrease in the side effects against the disadvantages of a possible recurrence of symptoms.

3. *Neuroleptic change:* High-dose neuroleptics such as the aliphatic (chlorpromazine) or piperidine (thioridazine) phenothiazines are less likely to cause acute extrapyramidal symptoms than the low-dose piperazine phenothiazines (trifluoperazine) or butyrophenones (haloperidol). (See Table 1.) Drugs less likely to cause acute side effects are also thought less likely to predispose to tardive dyskinesia.[4] However, the risk for non-CNS side effects (pigmentation, hepatitis and hypotension) may be increased with the high-dose drugs such as chlorpromazine. Mid-range neuroleptics such as pericyazine (Neuleptil®) and piperacetazine (Quide®) are relatively free of both types of side-effects.

TABLE 1
Neuroleptics Most Likely to Cause Extrapyramidal Syndromes

Most Likely	haloperidol
	fluphenazine
	trifluoperazine
	perphenazine
	pericyazine
	piperacetazine
	chlorpromazine
Least Likely	thioridazine
	methotrimeprazine

4. *Antiparkinsonian drugs:* In theory, dopamine agonists should be the treatment of choice in the acute extrapyramidal symptoms caused by neuroleptics, but are contraindicated because most of them will aggravate psychotic conditions. Anticholinergic parkinsonian drugs are effective in the neuroleptic-induced acute extrapyramidal side effects, but are contraindicated in tardive dyskinesia.

The antiparkinsonian drugs act primarily by blocking the muscarinic cholinergic receptors in the basal ganglia. An intramuscular dose can distinguish between acute EPS, which will improve, and TD, which will worsen. Antiparkinsonian agents should not be used prophylactically to prevent acute EPS. Idzorek,[11] and Swett[12] have independently shown that antiparkinsonian agents do not decrease the incidence or onset of extrapyramidal symptoms. Antiparkinsonian agents also carry considerable risks:

1. They cause cholinergic blockade of the peripheral, autonomic and central nervous systems, resulting in their own side effects such as dry mouth, constipation, urinary retention, hyperthermia and even psychosis.[13]
2. Antiparkinsonian agents may increase the incidence of TD, or cause other involuntary movements especially of the buccolingual-masticatory muscles.[14-16]
3. They may decrease the effectiveness of neuroleptics, perhaps by decreasing their absorption.[17-19]
4. They are prone to abuse because some patients use them as hallucinogens.[20] In suicide attempts, they are dangerously effective.

Differential Effects

The earliest drugs used for acute EPS include atropine, belladonna, scopolamine, stramonium and hyoscine. Even among these older drugs, a differential effect was noticed; scopolamine and hyoscine worked better for tremors, atropine and stramonium were better for rigidity and dystonias.[21, 22] Synthetic preparations are now more commonly used because they cause fewer side effects.

For dystonias and oculogyric crises, benztropine is effective and frequently used because it can be given parenterally both IM and IV.[23] However, it is strongly anticholinergic and may aggravate the dry mouth, constipation and urinary retention of neuroleptics. Benztropine is also sedating, has a long half-life and accumulates in the body; it should therefore be used very cautiously in the elderly.[21] It relieves the excessive saliva and drooling that occurs in drug-induced parkinsonism. The benzodiazepines such as diazepam are also very useful in acute drug-induced dystonias, even when anticholinergic parkinsonian agents fail.[24, 25] Diazepam may be a GABA agonist, which might result in an overall anticholinergic preponderance in the striatum and basal ganglia.[24]

Rigidity may also be treated with benztropine but trihexylphenidyl and procyclidine are more frequently used. They are less expensive and less sedating, have shorter half-lives and therefore are safer for the elderly.[21, 22] Divided doses are often necessary. Some investigators have commented on trihexylphenidyl's euphoric and hallucinogenic qualities.[20] It is sometimes activating and may be useful in the depressed or lethargic schizophrenic with side effects.

Tremors do not respond well to antiparkinsonian agents, although ethopropazine is said to be the most useful.[21, 22] Akathisia also does not respond well to most antiparkinsonian agents, but procyclidine is helpful in 50% of cases (benztropine and ethopropazine relieve only 20-25% of patients).[22]

When a patient has neuroleptic-induced parkinsonism and atropine side effects, amantadine may be very useful. It is the first dopamine agonist

which has been useful in drug-induced parkinsonism because it does not aggravate psychosis. It has very little anticholinergic activity and therefore will not aggravate dry mouth, blurred vision or constipation.[16] Gelenberg found it useful in neuroleptic-induced parkinsonism when other antiparkinsonism agents failed.[24] This drug may be particularly useful in patients taking neuroleptics and suffering from urinary retention, glaucoma and constipation, or who are elderly. Toxicity may occur with renal disease: 90% of the drug is excreted in the urine.[28]

Inadequate doses of antiparkinsonian agents are frequently prescribed and a family physician may increase the dose of side effect medication if parkinsonism persists. The maximum daily dose of benztropine is 8 mg per day and trihexylphenidyl, 15 mg per day. If an anticholinergic agent is used, the patient should be assessed for 'atropine' side effects which may warrant treatment. If the maximum safe dose of an antiparkinsonian agent does not control side effects, a trial of a second antiparkinsonian agent may be useful. The effective treatment of side effects will increase patient adherence to the treatment plan.

Expense

There can be a 300% increase in cost if trade names are used rather than generic names. In addition, the most expensive antiparkinsonian drug costs 14 times as much as the least expensive.

Withdrawal Effects

Most patients do not need their anticholinergic antiparkinsonian drug for more than three months, since acute EPS returns in only 8% of patients if the antiparkinsonian agent is stopped at that time.[29] Withdrawal effects seem to be minimal unless neuroleptics are withdrawn at the same time, which results in rebound cholinergic phenomena i.e. gastric secretion, hyperactivity, abdominal pain, colic, nausea and vomiting.[30]

Overdose

Overdosage of anticholinergic drugs may be very serious as they will produce a toxic 'atropine' psychosis, in which the patient is "dry as a bone, red as a beet, and mad as a hatter".[1] Because of the additive anticholinergic effects and cardiotoxicity, this is more likely to occur if the patient has also taken neuroleptics and antidepressants. Other signs of anticholinergic toxicity include acute brain syndrome, often with visual hallucinations and disorientation, dry mouth, blurred vision, dilated pupils, tachycardia, malignant arrhythmias, and no bowel sounds (paralytic ileus).

Physostigmine has been used to combat the central and peripheral effects of an anticholinergic overdose and is indicated when tachycardia and atropine psychosis occur.[31, 32] A 2 mg test dose of physostigmine can be given IM or slow IV. If there is no response, it may be repeated in 20-30 minutes. Improvement may be short lived because of the short half-life of physostigmine (one to two hours) compared to the long half-life of the anticholinergic drugs. This treatment can be continued until the clinical condition is stabilized or until physostigmine (cholinergic) toxicity is seen (constricted pupils, bradycardia, sweating, dyspnea, cramps, diarrhea and urinary frequency). Serious complications of physostigmine include heart block, provocation of an acute asthmatic attack, and aggravation of pre-existing medical conditions such as peptic ulcer, asthma, glaucoma, coronary artery disease and bowel or bladder obstruction.

Prevention and Treatment of Tardive Dyskinesia

Neuroleptics should not be used chronically for minor conditions. They should be reserved for serious recurrent or chronic forms of schizophrenia.[33] The lowest dose possible to keep a patient free from psychosis should be used. Anticholinergic antiparkinson drugs should be used only for specific side effects for short periods.

Once tardive dyskinesia is present, anticholinergics should be stopped and the neuroleptic slowly decreased or stopped if this is clinically possible. TD will usually diminish or disappear within three months after discontinuation. If a neuroleptic-free interval is not possible because of the clinical condition, the clinician must use the opposite strategy of increased neuroleptic dose in order to mask TD signs. Diazepam has been useful in tardive dyskinesia.[34] Amantadine has also been useful, as have other dopamine agonists.[4]

Treatment methods for tardive dyskinesia are largely experimental and are mainly aimed at correcting the acetylcholine-dopamine imbalance.[11, 35]

1. Depleting the dopamine with reserpine. The dose required is high and causes low blood pressure and depression.[4, 35]
2. Elevating acetylcholine levels by using lecithin or acetylcholine precursors.[4]

Conclusions

1. Signs of neuroleptic-induced parkinsonism and tardive dyskinesia are underreported and overlooked. Physicians should examine neuroleptic treated patients frequently and completely.
2. When extrapyramidal side effects are suspected, an intramuscular injection of an antiparkinsonian drug may be a useful diagnostic tool. If the motor disturbance worsens, tardive dyskinesia should be suspected.
3. Antiparkinsonian agents should not be used prophylactically.
4. Inadequate doses of antiparkinsonian agents are frequently prescribed.
5. Antiparkinsonian agents should not be continued indefinitely without indication.
6. If an anticholinergic agent is used, the patient should be assessed for 'atropine' side effects and these should be treated as necessary.
7. All antiparkinsonian agents are not the same. A patient with EPS may not respond to the first antiparkinsonian agent used; many patients can benefit from a second one.
8. Tardive dyskinesia can be minimized by restricting the use of long-term neuroleptics to conditions that do not respond to any other treatment. If neuroleptic maintenance is imperative, the dose should be kept as low as possible.
9. At the earliest signs of tardive dyskinesia, anticholinergic agents should be stopped and, if possible, the neuroleptic should be slowly discontinued. This is particularly important in older people, in whom TD is less readily reversible.[36]

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